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The Synthesis of Some Head to Head Linked DNA Minor Groove Binders

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Abstract—A series of head to head linked dimers of heterocyclic amino acids has been prepared for investigation of affinity and selectivity in binding to the minor groove of DNA. The selection of targets for synthesis was led by computer based design. Several novel dicarboxylic acid linkers including indoles, phenanthrenes, a fluorenone, and a bisbenzothiophene have been included. Analysis of binding to DNA by footprinting showed high affinity for compounds derived from 2,7-dihydrophenanthrene dicarboxylic acid and a predominant selectivity for AT rich regions containing at least 4 AT pairs but with the ability to span up to two CG base pairs.

The importance of nucleic acids as a target for drug action has been widely recognised and the potential benefits of controlling the biochemistry of an organism at the level of protein synthesis compared with enzyme inhibition emphasised.[1] A requirement for the effectiveness of drugs that act at nucleic acids is the ability to recognise defined sequences of DNA so that specific genes or control regions can be targeted. Moreover, high affinity for such sites is essential. Natural products such as distamycin are oligomers of heterocyclic amino acids and have been shown to bind to the minor groove of DNA displacing the hydrogen bonded water.[2] Typically they show a preference for AT rich regions and have dissociation constants of the order of 10^{-5} M.[3] Such compounds have intrinsic biological activity but they also have many limitations including toxicity, and low affinity, specificity, and solubility. Approaches to tackle the problems of affinity and specificity have centred on the introduction of additional monomers such as imidazole derivatives to promote CG reading,[4] on the linking of heterocyclic amino acids head to tail by aliphatic amino acids with flexible chains,[5] and on the linking of oligomers of heterocyclic amino acids head to head.[6] An approach from our laboratories to deal with problems of solubility and transport is described in another paper.[7] In this paper we describe the synthesis of a number of novel head to head linked oligomers of heterocyclic amino acids and demonstrate strong affinity when certain polycyclic aromatic compounds are used as linkers.

Selection of Compounds for Synthesis

In order to optimise affinity of minor groove binders such as the lexitropsins, it is necessary to maximise the hydrogen bonding between the NH of the carboxamides and the 2-carbonyl group of thymine and the 1N of adenine. The spacing of the NH groups in an extended lexitropsin does not closely match the positions of the hydrogen bond acceptors in DNA. Linking molecules were therefore designed to have the correct length and curvature to ensure that hydrogen bonding was possible using the pyrrole amino acid amides on both sides of the linker. A series of aromatic dicarboxylic acids was assessed for their ability to correct ligand misalignment with the DNA bases by computer simulation with an in vacuo DNA model using AMBER 4.0. Fig. 1 shows the shape of the dihydrophenanthrene linked compound in comparison with distamycin. The DNA phosphate groups were neutralised and the ligand termini were truncated to neutral $CONH_2$ groups. The ligands were docked into the minor groove of the hexadecamer $(d(A)\text{-}d(T))_{16}$ in the standard Arnott B-DNA conformation and minimised prior to molecular dynamics at 300 K for 200 ps. Geometries from dynamics trajectories were saved at 5 ps intervals for minimisation and subsequent energetic analysis of ligand internal energies and interaction energies between ligand and DNA. The internal energies of minimised isolated ligands were then subtracted from the ligand

Keywords: DNA; minor groove; lexitropsin dimer; synthesis.
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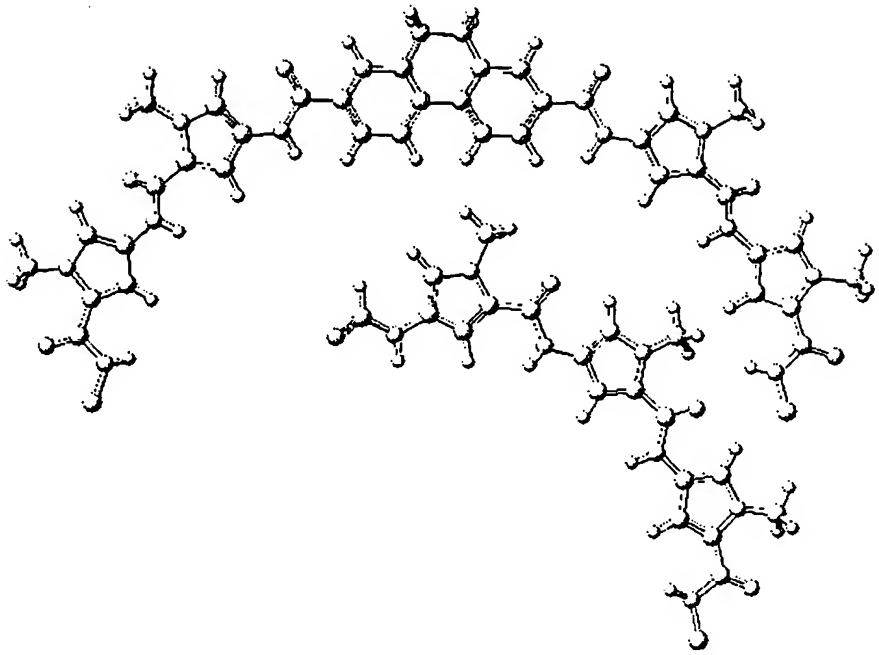


Figure 1. Molecular modelling representation of the cyclic portion of target molecules **19–24**, all of which contain a dihydrophenanthrene linker. The tripyrrole of distamycin is shown for comparison. The flexible side chains of both compounds are omitted for clarity. (Figures produced by molecular mechanics energy minimisation using the CACHE molecular modelling software system, Oxford Molecular.)

internal energies from simulation with the DNA model to give a quantitative measure of the ligand distortion upon binding. This distortion term was then added to the interaction energy for each ligand to give a corrected interaction energy, which was then used to rank the linker structures (Table 1). The interactions of cations with anionic sites with DNA was considered to be constant in the evaluation of the linkers themselves. One of the compounds included (**30**) has been synthesised before.[6]

To expand the structural repertoire, a number of compounds containing flexible components were also synthesised (indole derivatives and glycine derivatives: Table 1). For synthetic convenience, tertiary alkyl amines were commonly used as tail groups; this choice is also significant in the context of designing compounds with suitable solubility for use as drugs that will reach targets by passive diffusion.[7,8] Some amidines were also synthesised to provide congruence with previous work.[6] With the rigid linkers, all of these molecules would be expected to bind to DNA predominantly in a 1:1 manner unlike those in which extended flexible linkers such as GABA are included; in such cases, a hairpin or 2:1 structure is formed with an expanded minor groove which facilitates recognition of CG regions through hydrogen bonding to imidazole amino acids.[5]

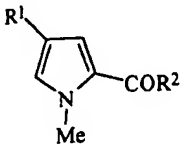
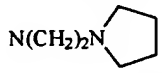
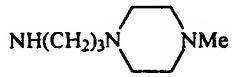
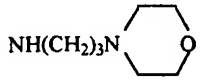
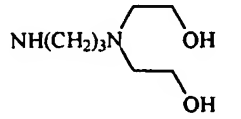
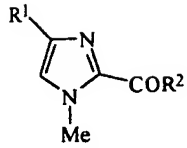
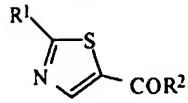
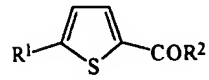
Synthesis of the Heterocyclic Amino Acid Oligomers

The monomeric heterocyclic amino acids (Table 2) were synthesised either directly by ring synthesis (for the thiazole **3**)[9] or by reduction of the corresponding nitro compound (for **1**,**2**,**4**).[10] The terminal carboxyl group was capped using either a monomer or a dimer as substrate with an aminopropyl amine or a cyanopropyl amine. The amidines were prepared by means of the Pinner reaction from the corresponding nitriles.[11] For the capping reactions of the

Table 1. Designed linkers and their calculated (and observed) interaction properties with DNA as shown by footprinting. Compounds marked * were investigated with amidinium headgroups; the remaining compounds had dimethylamino headgroups. Footprinting was carried out as described in Ref. 7. Strong footprint means that protection was observed at a ligand concentration of 0.3 μM; Good footprint refers to a concentration between 1 and 10 μM; '*nt*' means not tested in these experiments

Linker name and target compound number	Net interaction energy (units)	Rank	Observed interaction with DNA
Indole-2,6-dicarboxylate - flexible **33**	−108.9	1	Good footprint
Dihydrophenanthrene dicarboxylate **19**	−106.6	2	Strong footprint*
Bisbenzothiophene dicarboxylate **26**	−105.5	3	Strong footprint*
Phenanthrene dicarboxylic acid **25**	−103.5	4	*nt*
Indole-2,6-dicarboxylate-rigid **32**	−100.9	5	Good footprint
Terephthalic acid **28**	−100.4	6	Good footprint
Fumaric acid **29**	−95.1	7	Good footprint
Indole-2,5-dicarboxylate **35**	−92.6	8	Good footprint*
Indole-2,6-dicarboxylate **31**	−92.1	9	Weak footprint*
Trans-cyclopropane dicarboxylate **30**	−88.6	10	*nt*

Table 2. Monomers synthesised and their abbreviations

Structure	Substituents R^1	Substituents R^2	Abbreviation O_2N pyrr OEt	No.
	NO_2	OEt	O_2N pyrr OEt	**1a**
	NO_2	OH	O_2N pyrr OH	**b**
	NO_2	Cl	O_2N pyrr Cl	**c**
	NO_2	CCl_3	O_2N pyrr CCl_3	**d**
	NO_2	$NH(CH_2)_3NMe_2$	O_2N pyrr dmap	**e**
	NO_2		O_2N pyrr pyrp	**f**
	NO_2		O_2N pyrr mpip	**g**
	NO_2		O_2N pyrr morphp	**h**
	NO_2		O_2N pyrr dheap	**i**
	NO_2	OH	O_2N imid OH	**2a**
	NO_2	$NH(CH_2)_3NMe_2$	O_2N imid dmap	**b**
	NO_2	OEt	O_2N thia OH	**3a**
	NO_2	$NH(CH_2)_3NMe_2$	O_2N thia dmap	**b**
	NO_2	OH	O_2N thio OH	**4a**
	NO_2	$NH(CH_2)_3NMe_2$	O_2N thio dmap	**b**

imidazoles **2a**, pivalic anhydride mediated coupling was the best method found. For the pyrrole and thiophene derivatives, the amides were readily formed under Schotten Baumann conditions from the appropriate acid chloride typically in yields in excess of 85%. Alternatively 4-nitro-*N*-methylpyrrole 2-trichloromethyl ketone was an effective acylating agent for the synthesis of capped monomers.[12] Extension of the monomers to capped oligomers (**5–9**, Table 3) was essentially a two-stage process. Firstly the nitromonomer was hydrogenated using Pd–C as catalyst typically in methanol/ethylene glycol dimethyl ether (DME) mixtures or in DME alone. However not all compounds proved amenable to hydrogenation, the nitrothiophenes requiring extensive research to find appropriate reaction conditions. The amines thus produced were not isolated and purified but used directly for coupling with the second heterocyclic amino acid. The best conditions for coupling closely mirrored those found for the capping of the corresponding monomer. Coupling yields were in the range 58–95%, the best yields being obtained using acid chlorides. On the other hand, acid chlorides were not used in the preparation of the head to head linked compounds (see below).

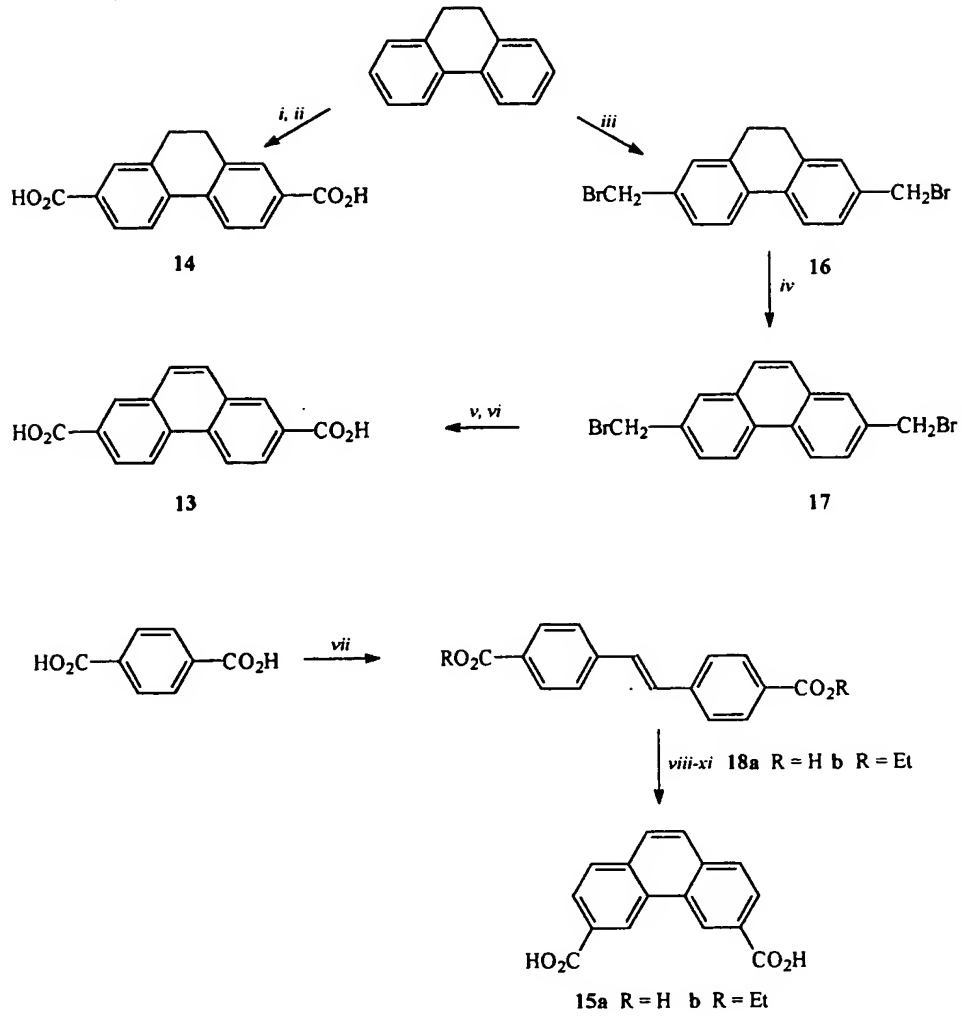
Table 3. Capped oligomers synthesised listed using abbreviations defined by structures in Table 2 above

Compound	No.	Compound	No.
O_2N pyrr pyrr dmap	**5a**	O_2N pyrr pyrr dheap	**5d**
O_2N pyrr pyrr pyrp	**5b**	O_2N pyrr pyrr morphp	**5e**
O_2N pyrr pyrr mpip	**5c**	O_2N pyrr pyrr amidp	**5f**
O_2N imid imid dmap	**6**	O_2N pyrr pyrr cyanp	**5g**
O_2N thio thio dmap	**7**	O_2N pyrr pyrr imidp	**5h**
O_2N pyrr thia dmap	**8**	Zgly pyrr pyrr dmap	**5i**
O_2N pyrr thio dmap	**9**	Gly pyrr pyrr dmap	**5j**

Synthesis of Linkers

The computational design suggested that (a) tricyclic aromatic compounds such as phenanthrene and fluorene derivatives and (b) 2,5- and 2,6-substituted indole dicarboxylic acids would be appropriate components. The synthesis of the phenanthrene derivatives is shown in Scheme 1. Substantial synthetic effort was required to obtain the indole dicarboxylic acids (**10a–e**, Table 4) and that work will be described in another paper.[13] Bisbenzothiophene-2,7-dicarboxylic acid **11** and fluorenone-2,7-dicarboxylic acid **12** were commercial samples.[14]

Three examples already described were included to provide controls (fumarate, *trans*-1,2-cyclopropane dicarboxylate, and terephthalate).[6] For phenanthrene derivatives (**13–15**, Scheme 1), dihydrophenanthrene was bisbromomethylated using paraformaldehyde in the presence of hydrobromic acid[15] to afford **16** which was dehydrogenated using



Scheme 1. *Reagents:* (i) CH_3COCl, $AlCl_3$; (ii) I_2, pyridine then NaOH/aq. EtOH; (iii) $(CH_2O)_n$, HBr, H_3PO_4 in aq HOAc; (iv) DDQ, benzene; (v) DMSO, $NaHCO_3$; (vi) $bipyH_2CrOCl_5$, CH_2Cl_2; (vii) S 270–275°C; (viii) $SOCl_2$; (ix) EtOH; (x) $h\nu$, I_2, O_2, toluene; (xi) aq NaOH.

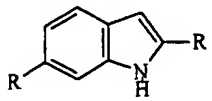
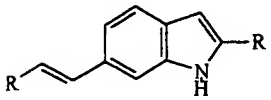
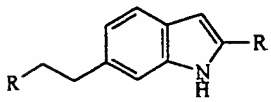
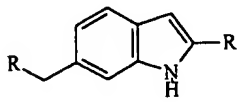
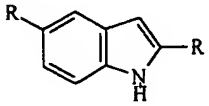
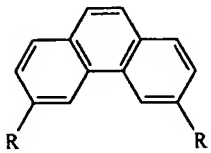
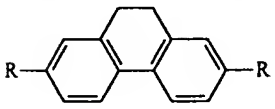
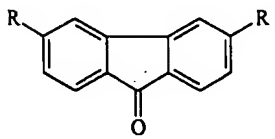
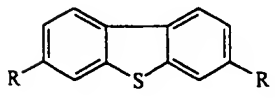
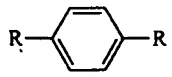
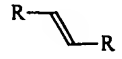
DDQ[15] to give 3,6-bisbromomethylphenanthrene **17** (40%). The required dicarboxylic acid **13** was obtained by sequential oxidation firstly with DMSO[16] to give the dialdehyde and secondly with chromium (VI)[17] (25% over 2 steps). The corresponding 3,6-dihydrophenanthrene dicarboxylate **14** was obtained in a separate synthesis by acetylation of dihydrophenanthrene itself under Friedel–Crafts conditions[18] to give the bismethylketone (24%) followed by oxidation to give the required diacid **14** and iodoform[19] (96%). The isomeric phenanthrene-2,7-dicarboxylic acid **15a** was prepared via pyrolysis of terephthalic acid in the presence of sulphur 270–275°C[20] to give the *trans*-stilbene-4,4′-dicarboxylate (**18a**, 20%). Conversion into the corresponding diethyl ester **18b** was carried out in two steps via the acid chloride (28–44%) and ethanolysis (79–87%). Photolysis in toluene solution in the presence of iodine and air[21] afforded diethyl phenanthrene-2,7-dicarboxylate **15b** (32%) and hydrolysis with aqueous sodium hydroxide gave the required phenanthrene dicarboxylic acid **15a** (99%).

Some linkers that seemed promising designs proved to be synthetically inaccessible. For example an approach to bisbenzofuran 3,7-dicarboxylic acid failed when the cyclisation of the precursor dimethyldihydroxybiphenyl with polyphosphoric acid afforded a cyclic phosphodiester (69%, Scheme 2) as the main isolable product.

Coupling of Dimers with Linker

The slight differences in reactivity and solubility between the various linkers meant that no single optimal method was found for the coupling reactions. This was true both of the hydrogenation of the nitro group of the precursor dimer and of the coupling reaction itself. For example, conditions for hydrogenating the bisimidazole intermediate **6** were crucial; a mixture of methanol and DMF (6:2.5 %) as solvent and a temperature of 40°C was found to be necessary. The most common methods used HBTU in the presence of *N*-methylmorpholine (Scheme 3).[23] In the case of the bisimidazole **6** the yield of isolated coupled product was only 5% after purification which contrasts with a yield of over 60% in the case of the flexible indole linker **10c** and the bispyrrole intermediate **5a**. Provided that sufficient material had been obtained for assay in DNA binding, optimisation experiments were not carried out in these couplings. The most difficult linkers to couple were the fully conjugated phenanthrene derivatives, perhaps because of the lower reactivity

Table 4. Linkers synthesised and their abbreviations

Structure (R = CO_2H throughout)	Abbreviation	No.
	*ind1*	**10a**
	*ind2*	**10b**
	*ind3*	**10c**
	*ind4*	**10d**
	*ind5*	**10e**
	*phen*	**13**
	*H$_2$phen*	**14**
	*fluo*	**12**
	*dbthia*	**11**
	*tere*	
	*fuma*	
	*t-cycp*	

of the corresponding carboxylic acids. The head to head dimers prepared are summarised in (Table 5). All products were purified using preparative HPLC under gradient elution conditions (see Experimental) and satisfactory NMR and electrospray mass spectra were obtained.

Affinity of Products for DNA

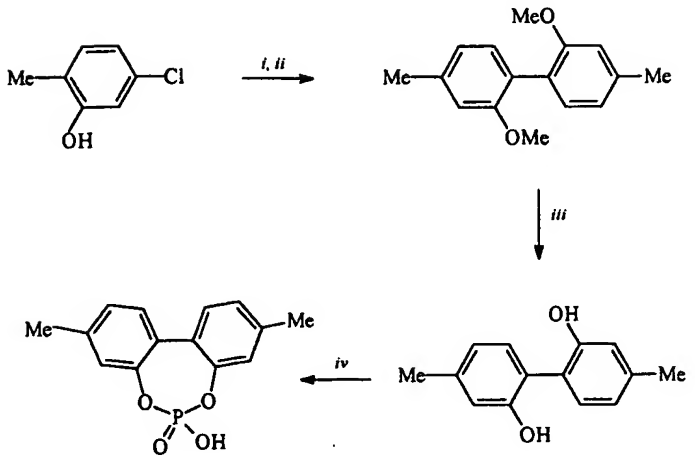
A small number of the compounds prepared have been evaluated in a preliminary study for their ability to bind to DNA;[7] we thank Dr Keith Fox (University of Southampton) for undertaking this study. Footprinting using TyrT DNA [24] as the target showed significant differences between the compounds studied. The fumaric acid linked compound **29** was studied in most detail; the results will be reported elsewhere.[7] The overall conclusion that can be drawn from the footprinting data is that these compounds are AT selective but cover larger regions than the parent antibiotic, distamycin. At moderate concentrations (~1 μM) there was evidence that they can span one or two CG base pairs. Using pAAD, pA_{3-6}, or pA/T_{3-12} DNA,[7] oligomers that offer a range of sizes of AT sites, the results suggested that more than four consecutive AT pairs are required to provide binding sites for these compounds. The tricyclic aromatic linkers, bisbenzothiophene **11** and dihydrophenanthrene **14**, gave compounds **26** and **19–25** with particularly strong binding at micromolar concentrations, principally to AT rich regions as would be expected. Similarly the indole 2,5-dicarboxylate derivative (**35** from **10e**) showed a strong footprint. On the other hand, 2,6-dicarboxylate analogues (**31–34** from **10a–d**) were comparatively poor binders. Although more detailed examination of these compounds is required, it is clear that the basic design strategy can lead to compounds of very high affinity for DNA. From the point of view of molecular design, compounds highly ranked such as **19–25** showed strong footprints but given the available binding data the modelling did not appear to have high predictive power. Moreover from the data available so far we cannot determine whether binding of the compounds containing polycyclic aromatic compounds involves intercalation. One of the benefits of using a polycyclic aromatic linker is that in principle, additional substituents can be added to modify solubility or to provide additional binding to DNA. Furthermore, it is possible to modify the synthetic routes to prepare asymmetric head to head linked compounds thereby expanding the ability to read defined sequences of DNA.

Experimental

The abbreviation used for each compound in the text and tables is given in the title line of each preparation in *italics*.

Instrumentation

Electrospray mass spectra (ES-MS) were obtained on a Fisons VG Platform Benchtop LC-MS. Electron impact (EI-MS) and fast atom bombardment (FAB-MS) mass spectra were obtained on a Jeol JMS-AX505HA mass spectrometer. NMR spectra were obtained on a Bruker AMX 400 spectrometer operating at 400 MHz for ^1H. In ^1H



Scheme 2. *Reagents:* (i) Me_2SO_4, NaOH; (ii) $NiCl_2ZnPPh_3$, α-dipy, DMF, 120°C; (iii) HBr/HOAc; (iv) polyphosphoric acid.

NMR spectra, the abbreviation 'exch.' signifies that the relevant resonances disappeared on treatment of the solution with D_2O.

HPLC purification of final products was carried out using a Vydac protein and peptide C18 column on a gradient eluting system. The solvents were *A*: water+0.1% trifluoroacetic acid, and *B*: acetonitrile 90%+water 10%+0.1% trifluoroacetic acid. The elution programme was as follows: (Table 6)

Preparation of monomers

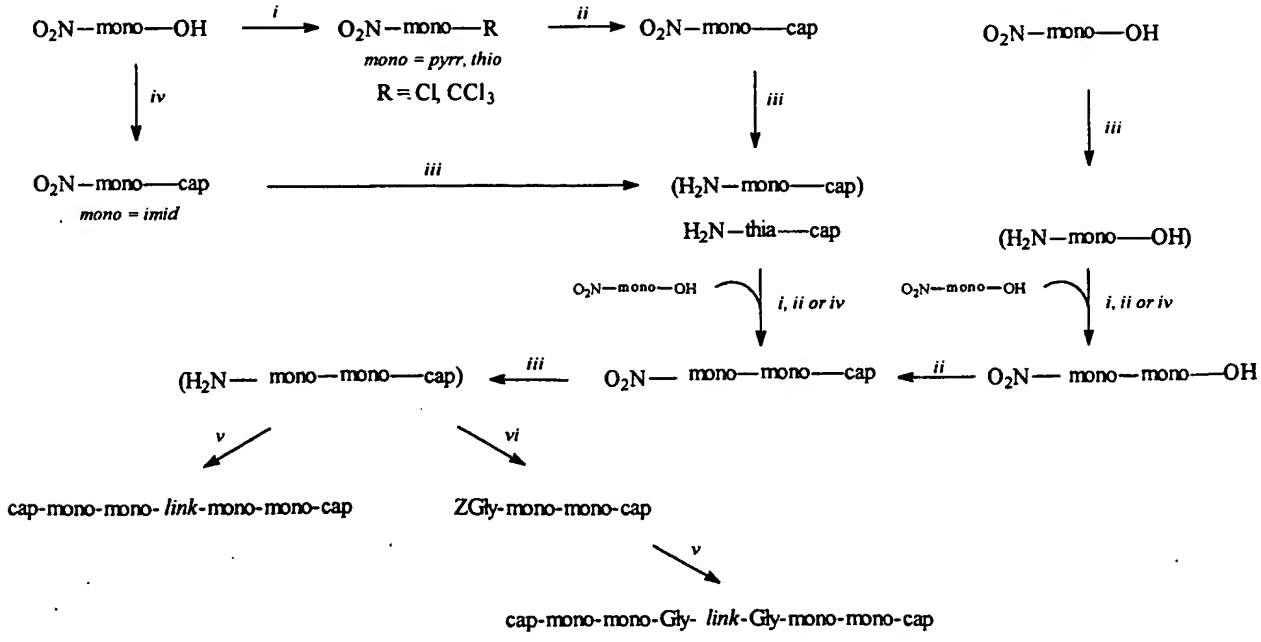
1-Methyl-4-nitropyrrole-2-carboxylic acid[4,5] (1b). (*O_2N pyrr OH*) This was prepared according to the literature[4,5] and obtained as a pale yellow powder (41% yield); mp 196–200°C (lit.[4] mp 204–205°C, lit.[6] mp 195–197°C).

1-Methyl-4-nitropyrrole-2-carbonyl chloride[10] (1c). (*O_2N pyrr Cl*) A standard literature procedure was used to give the product as grey solid material in quantitative yield, mp 90–91°C (lit.[10] mp 91–92°C). This acid chloride was used in the subsequent coupling without further purification.

1-Methyl-4-nitro-2-trichloroacetylpyrrole[9,10] (1d). (*O_2N pyrr CCl_3*) This was prepared in two steps from *N*-methylpyrrole by trichloroacetylation followed by nitration (96 and 41%, respectively) as pale yellow crystals mp 132–137°C (lit.[9] mp 135–140°C, lit.[10] mp 134–136°C).

3-(1-Methyl-4-nitropyrrole-2-carboxamido)dimethylaminopropane[11] (1e). (*O_2N pyrr dmap*) This was prepared using standard literature procedure. The product was obtained in (74% yield); mp 126–128°C (lit.[11] mp 126–127°C)

1-Methyl-4-(3-(1-methyl-4-nitropyrrole-2-carboxamido)-propyl)piperazine (1g). (*O_2N pyrr mpipp*) The pyrrole



Scheme 3. *Reagents:* (i) $SOCl_2$; (ii) amino or amidino cap, aq NaOH; (iii) H_2/Pd–C under solvent and temperature appropriate to each case (see Experimental); (iv) Me_3CCOCl, *N*-methylmorpholine, aminoacid cap; (v) HBTU, HOBT, *N*-methylmorpholine, *linker dicarboxylic acid*; (vi) HBTU, HOBT, ZglyOH.

Table 5. Head to head dimers synthesised

Compound	No.	Compound	No.
dmap pyrr pyrr *H₂phen* pyrr pyrr dmap	19	dmap pyrr pyrr *fuma* pyrr pyrr dmap	29
dheap pyrr pyrr *H₂phen* pyrr pyrr dheap	20	.....*t-cycp*.....	30
pyrp pyrr pyrr *H₂phen* pyrr pyrr pyrp	21	.....*ind1*.....	31
mpip pyrr pyrr *H₂phen* pyrr pyrr mpip	22	.....*ind2*.....	32
morphp pyrr pyrr *H₂phen* pyrr pyrr morphp	23	.....*ind3*.....	33
amidp pyrr pyrr *H₂phen* pyrr pyrr amidp	24	.....*ind4*.....	34
dmap pyrr pyrr *phen* pyrr pyrr dmap	25	.....*ind5*.....	35
.....*dbthi*.....	26	dmap imid imid *H₂phen* imid imid dmap	36
.....*fluo*.....	27	dmap thia pyrr *H₂phen* pyrr thia dmap	37
.....*tere*.....	28	dmap (pyrr)₂ Gly *phen* Gly (pyrr)₂ dmap	38

carboxylic acid **1c** (5.42 g, 31.9 mmol) was suspended in thionyl chloride (20 mL) and heated under reflux for 3 h. Excess thionyl chloride was removed under reduced pressure at room temperature then the remaining traces were co-evaporated with dichloromethane (30 mL, dry). *N*-methylpiperazine (5.00 g, 31.7 mmol) was diluted with dichloromethane (25 mL, dry) and added dropwise with stirring at 0°C to the solution of the acid chloride in dichloromethane (25 mL, dry). The reaction mixture was left stirring at room temperature overnight. The required *pyrrole carboxamide* precipitated as a yellow solid and filtered off, washed with dichloromethane (dry), and dried at 60°C under reduced pressure for 6 h (10.21 g, 93%.). Mp 185–188°C. ν_{max}/cm^{-1}(KBr) 1663, 1545, 1515, 1477, 1418, 1320. δ_H (DMSO-d_6): 1.72 (2H, s, CH_2); 2.51–3.26 (6H, m); 3.90 (3H, s, NMe pyrrole); 7.47 (1H, s, pyrrole); 8.13 (1H, s, pyrrole); 8.53 (1H, s, CONH exch.); 10.88 (1H, broad, HCl exch.). HRFABMS: Found: 310.18768 Calculated for $C_{14}H_{24}N_5O_3$ 310.18791.

4-(3-(1-Methyl-4-nitropyrrole-2-carboxamido)propyl)-morpholine (1h). (*O_2N pyrr morphp*) (a) *Acid chloride method:* A solution of **1c** (3.9 mmol: prepared as described earlier, from 2.36 g of the carboxylic acid **1b**), using 2.5 mL of thionyl chloride, and 10 mL of dimethoxyethane) in dry dimethoxyethane (20 mL) was cooled in an ice/water bath, and stirred while a solution of 4-(3-aminopropyl)morpholine (2.00 g, 13.9 mmol) in dry dimethoxyethane (5 mL) was added slowly during a period of 15 min. The resultant suspension was stirred at room temperature for 4 h, then diethyl ether (30 mL) was added. The solid was collected, washed with diethyl ether, and after drying under reduced pressure amounted to 3.88 g (84% yield of HCl salt of **1h**). This material was dissolved in water (100 mL) at about 50°C, and the solution was basified with 10% sodium carbonate (50 mL), and after cooling to 0°C, the precipitated solid was collected, and dried under reduced pressure to give the required *pyrrole carboxamide* (**1h**) as a fawn-coloured powder (0.875 g), mp 116–118°C; Found: C, 52.7; H, 7.05; N, 19.2% $C_{13}H_{20}N_5O_3$ requires: C, 52.69; H, 6.80; N, 18.91. ν_{max}/cm^{-1} (KBr) 3413, 3126, 2962, 2820, 1650, 1619, 1522, 1306, 1117; δ_H ($CDCl_3$) δ 1.79 (2H, m, CH_2–C*H_2*–CH_2), 2.54 (6H, m, 3×N–C*H_2*–CH_2), 3.50 (2H, q, J=6.0 Hz becoming t, J=6.2 Hz after D_2O, CONH–C*H_2*–CH_2), 3.77 (4H, t, J=4.5 Hz, CH_2–C*H_2*–O–C*H_2*–CH_2), 4.00 (3H, s, NC*H_3*), 7.10 (1H, d, J=1.6 Hz, Ar*H*), 7.55 (1H, d, J=1.6 Hz Ar*H*), 7.97 (1H, bs, exch., CON*H*). An additional 0.46 g of product (mp 112–116°C; IR identical to above) was obtained by extraction of the mother liquor with $CHCl_3$/methanol. The combined yield was 32%. (b) *Trichloroacetyl method:* A solution of 4-(3-aminopropyl)morpholine (2.93 g, 20.4 mmol) in dry THF (5 mL) was cooled in an ice/water bath, and stirred while a solution of 4-nitro-1-methyl-2-trichloroacetylpyrrole (**1d** 5.53 g, 20.4 mmol) in dry THF (15 mL) was added slowly during a period of 5 min. The solution was stirred at room temperature for 3 h, during which a solid separated out. Diethyl ether (40 mL) was added, and the solid was collected, washed with ether, and dried under reduced pressure to give the required *pyrrole carboxamide* (**1h**) (4.82 g, 80% yield) as a pale cream-coloured solid, mp 118–120°C. The mother liquor was evaporated under reduced pressure, and the residue was triturated with isopropanol to give additional sample (0.56 g, 9% yield) as a yellow solid, mp 118–120°C.

Table 6.

Step	Time (min)	Flow rate (mL min^{-1})	%A	%B
Equilibration	1	4	95	5
1	40	4	60	40
2	20	4	0	100
3	5	4	95	5
4	10	4	95	5

***N*-(3-(1-methyl-4-nitropyrrole-2-carboxamido)propyl)-diethanolamine (1i).** (*O_2N pyrr diheap*) A solution of *N*-(3-aminopropyl)-diethanolamine (500 mg, 3.086 mmol) in dry THF (2.0 mL) was cooled in an ice-water bath, and stirred while a solution of the trichloroacetyl pyrrole **1d** (837.5 mg, 3.086 mmol) in dry THF (2.0 mL) was added slowly over a period of 5 min. The mixture was stirred at room temperature for 20 h, then evaporated under reduced pressure to leave a golden yellow, syrupy residue. This was purified by flash column chomatography over silica, using a mixture of ethyl acetate (4 parts) and methanol containing 3% of conc. aq. ammonia solution (1 part) as eluant, to give the required *pyrrole carboxamide* **1i** as a yellow syrup (910 mg) which slowly crystallised. Recrystallisation from ethyl acetate/hexane gave pure **1i** as a pale yellow powder (594.8 mg, 61% yield), mp 80–82°C; ν_{max}/cm^{-1} (KBr) 3700–2500 (br), 3131, 2936, 2841, 1633, 1558, 1527, 1306, 1042; δ_H ($CDCl_3$) 1.78 (2H, m, CH_2–C*H_2*–CH_2), 2.64 (6H, m, 3×N–C*H_2*–CH_2), 3.50 (2H, q, J=4.6 Hz, becoming t, J=4.5 Hz after D_2O, NH–C*H_2*–CH_2), 3.67 (4H, t, J=4.6 Hz, 2×CH_2–C*H_2*-O), 3.98 (3H, s, N–C*H_3*), 7.23 (1H, d, J=1.6 Hz Ar*H*), 7.54 (1H, d, J=1.7 Hz Ar*H*);

(no signals were detected for N*H* or for 2×O*H*); ES-MS: 315.2; $C_{13}H_{22}N_4O_5$ requires 315.3 (M+1); HREIMS: Found: 314.15963 Calculated for $C_{13}H_{22}N_4O_5$ 314.15902.

3-(2-Carboxamido-1-methyl-4-nitroimidazole)dimethylaminopropane[24,25] (2b). (*O_2N imid dmap*) This was prepared using standard literature procedure. The product was obtained as yellow crystalline material in (60% yield); mp 140–142°C (lit.[24] mp 134°C; lit.[25] mp 210–211°C as HCl salt)

2-(5-Nitrothiophene-2-carboxamido)dimethylaminopropane (4b). (*O_2N thio dmap*) 5-Nitrothiophene 2-carboxylic acid (2.198 g, 12.69 mmol) was heated under reflux with thionyl chloride (10 mL) for 2 h, then the excess was removed under reduced pressure at 40°C. Dichloromethane (2×10 mL, dry) was added and removed under reduced pressure at 40°C. 3-Dimethylaminopropylamine (1.357 g, 13.28 mmol) was dissolved in dichloromethane (5 mL, dry) and added to a solution of the acid chloride in dichloromethane (25 mL, dry) dropwise, at 0°C with stirring. The yellow suspension that formed immediately was left stirring and allowed to warm to room temperature. The reaction mixture was extracted with water and the aqueous layer was basified with sodium carbonate. The yellow oil that precipitated was extracted with ethyl acetate, dried, and filtered, then the solvent was removed under reduced pressure at room temperature to give the required *thiophene carboxamide* as yellow crystals (2.21 g, 68% yield). Mp 102–104°C. (Found: C,46.6; H,5.9; N,16.2; S,12.3 $C_{10}H_{15}N_3O_3S$ requires C,46.7; H,5.9; N,16.3; S,12.5.) ν_{max}/cm^{-1} (KBr): 3336, 1628, 1563, 1534, 1514, 1355, 1340, 1320, 1302. δ_H (DMSO-d_6): 1.73–1.82 (2H, qt, *J*= 6.9 Hz, CH_2); 2.34 (6H, s, NMe_2); 2.57–2.59 (2H, t, 1.6 Hz, CH_2); 3.53–3.59 (2H, qt, *J*=4.5 Hz, CH_2); 7.29–7.31 (1H, d, *J*=1.5 Hz, ArH); 7.85–7.86 (1H, d, 1.5 Hz, ArH); 9.40 (1H, broad CONH exch.).

Preparation of dimers

3-[1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)-pyrrole-2-carboxamido]dimethylaminopropane[11] (5a). (*O_2N pyrr pyrr dmap*) This was prepared using standard literature procedure. The product was obtained as pale yellow crystalline material in (79% yield); mp 190–192°C (lit.[11] mp 193–194°C).

1-Methyl-4-(3-(1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido)propyl)piperazine (5c). (*O_2N pyrr pyrr mpipp*) The *N*-methylpiperazine amide hydrochloride **1g** (0.684 g, 1.966 mmol) was dissolved in ethanol (20 mL) and HCl (10 mL, dil). This solution was hydrogenated using Pd/C (256 mg, 10%) at room temperature and atmospheric pressure overnight. Filtration and washing the catalyst with water (10 mL) gave a pale yellow solution which was evaporated under reduced pressure at room temperature to give a pale yellow oil. This oil was dissolved in water (10 mL), to which was added gradually with stirring sodium hydrogen carbonate (1.305 g). The acid chloride was prepared from the carboxylic acid **1b** (406 mg, 2.39 mmol) heated under reflux in thionyl chloride (1 mL) and dimethoxyethane (5 mL, dry) for 2 h. The solvent was removed under reduced pressure at 40°C, then dissolved in benzene (10 mL), this solution was added dropwise with stirring at room temperature to the solution of **1g**. The resulting mixture was heated under reflux for 1/2 h. then left to cool to room temperature and stirring was continued overnight. The reaction mixture was extracted with dichloromethane, dried and solvent removed under reduced pressure to give yellow solid product (806 mg, 95%). This product was purified by flash column chomatography using silica gel and ethyl acetate/methanol/ammonium hydroxide (49%/49%/2%). TLC: R_f=0.2. Mp 175–177°C (from benzene/*n*-hexane). HREIMS: Found: 431.22612 Calculated for $C_{20}H_{29}N_7O_4$ 431.22810; ν_{max}/cm^{-1} (KBr): 1667, 1635, 1578, 1564, 1543, 1493, 1320. δ_H($CDCl_3$): 1.70–1.80 (2H, qt, *J*=6.9 Hz, CH_2); 2.29 (3H, s, NMe); 2.41–2.53 (10H, m); 3.43–3.50 (2H, q, *J*=6.1 Hz, CH_2); 3.91 (3H, s, NMe pyrrole); 4.04 (3H, s, NMe pyrrole); 6.66 (1H, d, *J*=1.7 Hz, pyrrole); 7.11 (1H, d, *J*=1.6 Hz, pyrrole); 7.26 and 7.27 (1H, d, *J*=1.6 Hz, pyrrole); 7.34–7.38 (1H, t, *J*=5.5 Hz, CONH exch.); 7.60 and 7.61 (1H, d, 1.8 Hz, pyrrole); 7.84 (1H, s, CONH exch.).

***N*-(3-(1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)-pyrrole-2-carboxamido)propyl)diethanolamine (5d).** (*O_2N pyrr pyrr dheap*) A mixture of the nitropyrrole amide (**1i**) (549 mg, 1.75 mol), 10% Pd–C (202 mg) and isopropanol (25 mL) was hydrogenated at room temperature for 5 h. The catalyst was removed by filtration through kieselguhr, and the filtrate was evaporated under reduced pressure. The green, oily residue was dissolved in dry DMF (2.0 mL), and the solution was cooled in an ice-water bath while a solution of the trichloroacetyl pyrrole **1d** (474 mg, 1.75 mmol) in dry DMF (1.0 mL) was added slowly during a period of 5 min. The resultant solution was stirred at room temperature for 16 h, then it was chomatographed over a flash column of silica, using a mixture of ethyl acetate (4 parts) and methanol containing 3% of conc. ammonium hydroxide (1 part) as eluant, to afford the required *amide* **5d** as an amber gum (307 mg, 40% yield). HRFABMS: Found: 437.21360 Calculated for $C_{19}H_{29}N_6O_6$ 437.21485; δ_H ($CDCl_3$) 1.74 (2H, m, CH_2–C*H*$_2$–CH_2), 2.67 (6H, m, 3×N–C*H*$_2$–CH_2), 3.43 (2H, q, 6.1 Hz, becoming t, *J*=3.5 Hz after D_2O, NH–CH_2–C*H*$_2$), 3.67 (4H, t, *J*= 3.5 Hz, 2×CH_2–C*H*$_2$–OH), 3.86 (3H, s, NMe), 4.01 (3H, s, NMe), 6.71 (1H, d, *J*=1.6 Hz, Ar*H*), 7.08 (1H, t, *J*= 5.5 Hz, exch., CON*H*–CH_2), 7.17 (1H, d, *J*=1.6 Hz, Ar*H*), 7.42 (1H, d, *J*=1.6 Hz, Ar*H*), 7.57 (1H, d, *J*= 1.6 Hz, Ar*H*), 8.92 (1H, s, exch., CON*H*).

4-(3-(1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)-pyrrole-2-carboxamido)propyl)morpholine (5e). (*O_2N pyrr pyrr morphp*) A mixture of the nitropyrrole morpholine amide **1h** (1.30 g, 4.39 mmol.) and 10% Pd–C (510 mg) in isopropanol (50 mL) was hydrogenated at room temperature for 5 h. The catalyst was removed by filtration though kieselguhr, and the filtrate was evaporated under reduced pressure. Traces of isopropanol were removed from the residue by co-evaporation with dimethoxyethane (5 mL), to leave an amber oil. This oil was dissolved in dry dimethoxyethane (5 mL), and the solution was cooled in an ice/water bath, and stirred while a solution of the trichloroacetyl pyrrole **1d** (1.19 g, 4.39 mmol.) in a mixture of dry dimethoxyethane (2 mL) and dry THF (1.5 mL) was slowly added over a period of 5 min. The resultant solution

was stirred at room temperature for 16 h, then evaporated under reduced pressure. The semisolid residue was triturated with isopropanol until it solidified. The solid was collected, washed with isopropanol (5 mL) and dried under reduced pressure to give the required *amide* **5e** as a yellow powder (1.09 g, 59%), mp 182–184°C. HREIMS: Found: 418.19716 Calculated for $C_{19}H_{26}N_6O_6$ 418.19647; ν_{max}/cm^{-1} (KBr) 3408, 3125, 1656, 1634, 1574, 1535, 1502, 1309, 1116, 1110; δ_H (DMSO-d_6): 1.57–1.69 (2H, qt, J=7.0 Hz); 2.27–2.30 (6H, m); 3.15–3.27 (2H, q, J=6.0 Hz); 3.55–3.59 (4H, t, J=4.6 Hz); 3.80 (3H, s, NMe); 3.95 (3H, s, NMe); 6.83–6.84 (1H, d, J=1.7 Hz); 7.19–7.20 (1H, d, J=1.6 Hz); 7.56–7.57 (1H, d, J=1.8 Hz); 8.05–8.09 (1H, t, J=5.6 Hz, CONH exch.); 8.17–8.18 (1H, d, J=1.8 Hz); 10.23 (1H, s CONH exch.).

3-[1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)-pyrrole-2-carboxamido)propionitrile[4,13] (5g). (*O_2N pyrr pyrr cyanp*) This was prepared using standard literature procedure. The product was obtained as yellow powder in (87% yield); mp 228–230°C (lit.[4] mp 230–232°C; lit.[13] mp 254–255°C).

Ethyl 3-[1-methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)pyrrole-2-carboxamido]propionimidate hydrochloride (5h). (*O_2N pyrr pyrr imidp*) A suspension of the foregoing nitrile **5g** (6.44 g) in anhydrous ethanol (250 mL) was cooled and stirred, and saturated at −20°C with dry HCl(g). The resultant mixture was stirred at room temperature for 3 h, then evaporated under reduced pressure. The residue was triturated with dry diethyl ether, decanted and dried under reduced pressure to give the required imidate **5h** (7.93 g, 99% yield) as a yellow solid; mp 134°C (decomp.). This was used in the next step without further purification.

3-[1-Methyl-4-(1-methyl-4-nitropyrrole-2-carboxamido)-pyrrole-2-carboxamido]propionamidine hydrochloride[4,11,12] (5f). (*O_2N pyrr pyrr amidp*) A suspension of the above imidate **5h** (3.345 g) in anhydrous ethanol (100 mL) was stirred and cooled to −78°C in an acetone–dry ice bath. Liquid ammonia (75 mL) was added, and the resultant mixture was allowed to warm up slowly to room temperature. A clear solution formed, from which a solid separated overnight. The precipitate was collected, washed with ethanol, then with diethyl ether, and dried under reduced pressure to give the required amidine (2.30 g, 74% yield) as a yellow powder; mp 308°C (decomp.). [Lit.[4] mp 315°C (decomp.), lit.[12] mp 324–325°C]. A further sample was prepared following the literature[11] in 69% yield mp 314–315°C [lit.[11] mp 246°C]. (Found: C, 54.4; H, 6.15; N, 19.9%; $C_{19}H_{26}N_6O$ requires: C, 54.54; H, 6.26; N, 20.08%.) δ_H (DMSO-d_6) 1.64 (2H, m, CH_2–CH_2–CH_2), 2.33 (6H, m, 3×N–CH_2–CH_2), 3.20 (2H, q, J=6.2 Hz becoming t, J=6.1 Hz, after D_2O, CONH– CH_2–CH_2), 3.57 (4H, t, J=4.7 Hz, CH_2–CH_2–O–CH_2–CH_2), 3.80 (3H, s, pyrrole NMe), 3.95 (3H, s, pyrrole NMe), 6.84 (1H, d, J=1.7 Hz, Ar*H*), 7.20 (1H, d, J=1.8 Hz, Ar*H*), 8.07 (1H, t, J=5.5 Hz, exch., CON*H*–CH_2), 8.18 (1H, d, J=1.7 Hz, Ar*H*), 10.24 (1H, s, exch., CON*H*).

3-{Carbobenzoxyglycyl-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]} dimethylaminopropane (5i). (*Z Gly pyrr pyrr dmap*) A mixture of the nitropyrrole dimer **5a** (*O_2N pyrr pyrr dmap* 750 mg) and 10% Pd–C (690 mg) in isopropanol (75 mL) was hydrogenated at room temperature for 5 h. The catalyst was removed by filtration under an atmosphere of nitrogen, and the filtrate was evaporated under reduced pressure to leave crude amine as a greenish grey, glassy residue (631 mg, 91% yield), which was used immediately without further purification.

A mixture of carbobenzoxyglycine (457 mg, 2.19 mmol), HBTU (829 mg, 2.19 mmol), NMM (725 μL, =663 mg, 6.56 mmol.), and dry DMF (2.5 mL) was placed under nitrogen and stirred at room temperature for 30 min. To the resultant, clear solution was added a solution of the crude amine (631 mg, 1.82 mmol) in dry DMF (4 mL) slowly over a period of 5 min. The solution was stirred at room temperature for 15 h, then it was added to ethyl acetate (200 mL), extracted with 5% aqueous sodium carbonate solution (50 mL), washed with brine, and dried (Na_2SO_4) then evaporated under reduced pressure. The oily residue was dissolved in methanol, and the solution was passed though a short column of neutral alumina using methanol to elute the product which was used directly for the following preparation.

3-{Glycyl-[1-methyl-4-(4-amino-1-methylpyrrole-2-carboxamido)pyrrole-2-carboxamido]}dimethylaminopropane (5j). (*Gly pyrr pyrr dmap*) A mixture of foregoing trimer and 10% Pd–C (300 mg) in isopropanol (30 mL) was hydrogenated at 60°C for 15 h. The catalyst was removed by filtration though kieselguhr, and the filtrate was evaporated under reduced pressure to leave the deprotected trimer as an amber, gummy residue (196 mg, 82%); HPLC showed the material to be 90% pure and no unreacted starting material was detected. (Found ES-MS; 403.77, 201.46: $C_{19}H_{29}N_7O_3$ requires 404.5 (M+1), 202.75 [(M+2)/2]. The crude product was used immediately without further purification for the preparation of compound **38** below.

3-[1-Methyl-4-(1-methyl-4-nitroimidazol-2-carboxamido)-imidazol-2-carboxamido]dimethylaminopropane[25] (6). (*O_2N imid imid dmap*) This was prepared using standard literature procedure. The product was obtained as yellow solid in (58% yield); mp 160–161°C as HCl salt (lit.[25] mp 161–165°C as HCl salt).

3-[5-(5-Nitrothiophene-2-carboxamido)thiophene-2-carboxamido]dimethylaminopropane (7). (*O_2N thio thio dmap*) 3-(5-Nitrothiophene-2-carboxamido)dimethylaminopropane **4c** (226 mg, 0.879 mmol) and Pd/C (293 mg, 10%) were suspended in isopropanol (25 mL) and hydrogenated for 5 h. The reaction mixture was filtered through kieselguhr under nitrogen and the solvent was removed under reduced pressure. The acid chloride was prepared from 5-nitrothiophene-2-carboxylic acid **4a** (212 mg, 1.22 mmol) by heating under reflux for 3 h with thionyl chloride (3 mL). The excess thionyl chloride was removed under reduced pressure and the traces of thionyl chloride were removed by co-evaporation with dichloromethane. The amine produced by hydrogenation was dissolved in dichloromethane (3 mL, dry) and added dropwise at 0°C to a solution of the acid chloride in

dichloromethane (2 mL, dry). The reaction mixture was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the yellow residual solid suspended in brine and extracted with ethyl acetate. The aqueous layer was basified with aq. sodium carbonate solution then extracted with ethyl acetate, the organic layer dried ($MgSO_4$) and the solvent removed under reduced pressure to give the required *amide dimer* (199 mg, 59% yield) as a dark brown solid, mp 185–190°C (softening). HRFABMS: Found: 383.08482 Calculated for $C_{15}H_{19}N_4O_4S_2$ 383.08477; ν_{max}/cm^{-1} (KBr) 1657, 1623, 1536, 1502, 1462, 1334, 1300. δ_H (DMSO-d_6): 1.64–1.76 (2H, qt, J=7.1 Hz, CH_2); 2.49–2.51 (2H, t, J=4.7 Hz, CH_2); 3.17–3.28 (2H, q, J=6.1 Hz, CH_2); 6.82 and 6.84 (1H, d, J=2.1 Hz, thiophene H); 7.22 and 7.24 (1H, d, J=2.1 Hz, thiophene H); 7.91 and 7.93 (1H, d, J=2.1 Hz, thiophene H); 8.17 and 8.18 (1H, d, J=2.1 Hz, thiophene H); 8.33–8.37 (1H, t, J=5.7 Hz, CONH exch.).

3-[4-Methyl-2-[(1-methyl-4-nitropyrrole-2-carboxamido)-thiazole-5-carboxamido](*N*,*N*-dimethyl)propanamine (8). (*O_2N pyrr thia dmap*) 4-Methyl-2-(1-methyl-4-nitropyrrole-2-carboxamido)thiazole-5-carboxylic acid (**3a**) (0.400 g, 1.289 mmol) was dissolved in benzene (40 mL, dry) and thionyl chloride (3 mL, freshly distilled) and heated under reflux for 4 h. The solvent was removed under reduced pressure, and the residue was co-evaporated with hexane (25×3 mL, dry). The product was used without any further purification. A cooled solution of *N*,*N*-dimethylaminopropylamine (350 μL, 2.781 mmol) and triethylamine (1 mL) in dichloromethane (20 mL, dry) was added dropwise to the above acid chloride in THF (25 mL, dry) under nitrogen. After the reaction mixture was stirred at room temperature for 12 h, the solvent was removed under reduced pressure and the resulting residue was extracted in a 1:1 mixture of THF:ethyl acetate (2×100 mL) and dil. solution of sodium bicarbonate. The organic layer was washed with brine, dried, and evaporated under reduced pressure at room temperature. The crude product was purified on a column of silica gel (methanol/ethyl acetate 1:1). The second fraction was collected and on evaporation afforded the required *amide* **8** (255 mg, 50%) as yellow crystals, mp 204–206°C. R_f=0.15 (silica, 1:1 methanol:ethyl acetate). HRFABMS: Found: 395.15210 Calculated for $C_{16}H_{23}N_6O_4S$ 395.15015; ν_{max}/cm^{-1} (KBr) 1625, 1502, 1430, 1430, 1378, 1316. δ_H (DMSO-d_6) 1.55–1.65 (2H, qt, J=7.1 Hz, CH_2); 2.15–2.25 (6H, s, NMe_2); 2.26–2.39 (2H, t, 4.6 Hz, CH_2); 2.50 (3H, s, thiazole-Me); 3.15–3.28 (2H, q, J=5.9 Hz, CH_2); 3.95–4.50 (3H, s, pyrrole-Me); 7.75–7.90 (1H, d, 2.2 Hz, ArH); 8.02–8.06 (1H, t, J=5.7 Hz, NH, exch.); 8.26 (1H, s, ArH).

3-[5-(4-Nitro-*N*-methylpyrrole-2-carboxamido)thiophene-2-carboxamido]dimethylaminopropane (9). (*O_2N pyrr thio dmap*) 4-Nitro-*N*-methylpyrrole-2-carboxylic acid **1b** (190 mg, 1.117 mmol) was suspended in thionyl chloride (4 mL) and heated under reflux for 1.5 h. Excess thionyl chloride was removed under reduced pressure and the last traces of it were removed by co-evaporation with dichloromethane (2×5 mL, dry). 2-(5-Nitrothiophene-2-carboxamido) dimethylaminopropane **4c** (205 mg, 0.797 mmol) and Pd/C (207 mg, 10%) were suspended in isopropanol (25 mL) and hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration over kieselguhr under nitrogen, then the solvent was removed under reduced pressure at 40°C. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which was added the acid chloride **1c** dissolved in dichloromethane (10 mL, dry) dropwise at 0°C. Stirring was continued overnight while the temperature was left to rise to room temperature The product precipitated as a yellow solid; it was filtered off, and washed with a small amount of dichloromethane (dry) to give the required *amide* **9** (163 mg, 50%). Mp>230°C. Some of this material was further purified by HPLC for characterisation. HRFABMS: Found: 380.13854 Calculated for $C_{16}H_{22}N_5O_4S$ 380.13925; ν_{max}/cm^{-1} (KBr): 1670, 1641, 1624, 1533, 1459, 1310, 1288. δ_H (DMSO-d_6): 1.84–1.88 (2H, qt, J=7.1 Hz, CH_2); 2.79 (6H, s, NMe_2); 3.08 (2H, t, J=4.7 Hz, CH_2); 3.08–3.29 (2H, q, J=6.2 Hz, CH_2); 3.98 (3H, s, NMe pyrrole); 6.84 and 6.85 (1H, d, 2.1 Hz); 7.54 and 7.55 (1H, d, J=2.0 Hz); 7.73 and 7.74 (1H, d, J=1.9 Hz); 8.28 and 8.28 (1H, d, 1.8 Hz); 8.43–8.46 (1H, t, J=5.5 Hz, CONH exch); 9.31 (1H, broad TFA exch); 11.65 (1H, s, CONH exch.).

Preparation of linkers

2,7-Bis(bromomethyl)-9,10-dihydrophenanthrene[15,16] (16). Literature procedures[15,16] were adapted as follows. A mixture of 9,10-dihydrophenanthene (20.11 g), paraformaldehyde (14.72 g), 85% phosphoric acid (22 mL), 48% aq. hydrogen bromide (38.5 mL), and 30% hydrogen bromide in acetic acid (44 mL) was placed under nitrogen and stirred and heated at 80°C for 21 h, then at 117°C (gentle reflux) for 5 h., and allowed to cool. The crude product separated as a grey solid mass. The supernatant liquid was decanted and the solid stirred with acetone (100 mL) at room temperature for 18 h, then cooled to 0°C. The insoluble solid was collected, washed with cold acetone, and recrystallised from benzene/petroleum ether (bp 40–60°C) to give the required dibromodihydrophenanthrene **16** as an off-white powder (16.23 g, 40% yield); mp 150–154°C (lit.[15] mp 157–158°C, lit.[16] mp 150–151°C); ν_{max}/cm^{-1} (KBr) 3414, 2925, 2896, 2830, 1640, 1618, 1488, 1243, 1205 cm^{-1}. δ_H ($CDCl_3$) 2.87 (4H, s, CH_2–CH_2), 4.53 (4H, s, 2×Ar–CH_2–Br), 7.28 (2H, s, Ar*H*), 7.33 (2H, d, J=8.0 Hz, Ar*H*), 7.71 (2H, d, 8.0 Hz, Ar*H*).

2,7-Diacetyl-9,10-dihydrophenanthene.[17,19] Literature procedures[17,19] for the Friedel–Crafts acetylation of 9,10-dihydrophenanthene were adapted as follows. Acetyl chloride (9.15 g, 117 mmol) was added with stirring using a motor-driven paddle stirrer to a suspension of aluminium trichloride (15.56 g, 117 mmol) in dry dichloromethane (75 mL), and the resultant solution was heated in a bath at a controlled temperature of 40°C, keeping the solvent just below the point of reflux. A solution of 9,10-dihydrophenanthene (9.54 g, 53.0 mmol) in dry dichloromethane (35 mL) was added dropwise over a period of 2 h, keeping the solvent just below refluxing temperature. Stirring was continued for a further 1 h at 40°C, then for 18 h at room temperature. The mixture was cooled in ice, and a solution of HCl (20 mL conc. HCl diluted with 30 mL water) was added slowly with vigorous stirring. An additional 50 mL of water was introduced to overcome emulsification and the layers were allowed to separate. The organic layer was

washed with 10% aq. sodium carbonate (250 mL), then with brine (100 mL), then dried (Na_2SO_4), and evaporated to leave an oil (15.25 g) which solidified slowly. This residue was stirred with acetone (20 mL) at room temperature for 1 h, and the solid was filtered off and washed with a little cold (−15°C) acetone. This crude product (7.78 g) was recrystallised from hot ethanol (100 mL) to afford 3.91 g of partially purified product, mp 138–142°C. Further recrystallisation from ethanol (60 mL) afforded the required diacetyldihydrophenanthrene, as golden yellow glistening plates (3.36 g, 24%) mp 142–144°C (lit.[17] mp 144–144.5°C); ν_{max}/cm^{-1} (KBr) 1681, 1677, 1641, 1603, 1262; δ_H ($CDCl_3$) 2.64 (6H, s, 2×CH_3CO), 2.98 (4H, s, CH_2–CH_2), 7.82–7.97 (6H, m, Ar*H*).

9,10-Dihydrophenanthrene-2,7-dicarboxylic acid[17] (14). The foregoing diketone was oxidised with iodine via its bispyridinium salt according to a literature procedure,[17] to give the crude diacid (**14**) as a dark brown powder (96% mp>350°C). Recrystallisation from aqueous DMF (decolourising charcoal) gave a lighter brown product, mp>360°C (lit.[17] mp~350°C); ν_{max}/cm^{-1} (KBr) 1686, 1640, 1613, 834; δ_H (DMSO-d_6) 2.90 (4H, s, CH_2–CH_2), 7.87–8.01 (6H, m, Ar*H*)

2,7-Bis(bromomethyl)phenanthrene (17). A mixture of the bisbromomethyldihydrophenanthrene (**16**, 4.62 g, 12.6 mmol), DDQ (3.15 g) and dry benzene (30 mL) was heated under reflux for 18 h. The mixture was filtered while still hot though a 2.5 in. column of neutral alumina, rinsing with hot benzene. The filtrate was evaporated under reduced pressure, and the residue was crystallised from benzene/petroleum ether (bp 40–60°C) to give the required *bisbromomethylphenanthrene* as pale buff-coloured crystals (2.94 g, 64% yield); mp 189–191°C. (Found: C, 52.9; H, 3.3; Br, 43.7%. $C_{16}H_{12}Br_2$ requires C, 52.78; H, 3.32; Br, 43.90%). ν_{max}/cm^{-1} (KBr) 1638, 1260, 1212, 1202, 906, 811 cm^{-1}; δ_H ($CDCl_3$) 4.73 (4H, s, 2×ArCH_2Br), 7.68–7.74 (4H, m, 4×Ar*H*), 7.90 (2H, d, *J*=1.7 Hz, 2×Ar*H*), 8.65 (2H, d, *J*=8.6 Hz, 2×Ar*H*).

2,7-Diformylphenanthrene.[26] This was prepared using standard literature procedure. The crude product was purified by flash column chromatography (SiO_2/dichloromethane) to give the required diformylphenathrene as bright yellow crystals in (52% yield), mp >350°C; ν_{max}/cm^{-1} (KBr) 1690, 1639, 1617, 1575 cm^{-1}. δ_H ($CDCl_3$) 7.95 (2H, s, 2×Ar*H*), 8.16–8.21 (2H, dd, *J*=1.7 Hz and 8.6 Hz 2×Ar*H*), 8.42 (2H, d, *J*=1.6 Hz, 2×Ar*H*), 8.84 (2H, d, *J*=8.6 Hz, 2×Ar*H*), 10.25 (2H, s, 2×Ar*CH*O).

Phenanthrene-2,7-dicarboxylic acid[27] (13). The reagent (bipy)H_2CrOCl_5 reagent was freshly prepared according to the literature procedure[20] as a brown powder (31% yield). A solution of the foregoing dialdehyde (516 mg, 2.20 mmol) in dry dichloromethane (50 mL) was placed under nitrogen, and stirred at room temperature. (Bipy)H_2CrOCl_5 (4.45 g, 11.02 mmol) was added, and the mixture was stirred at room temperature for 18 h, then evaporated under reduced pressure. The residue was extracted *cautiously* (CO_2!) with a solution of sodium hydrogen carbonate (10 g) in water (250 mL). Some insoluble material was removed by filtration through kieselguhr, and the filtrate was acidified *cautiously* (CO_2!) with conc. hydrochloric acid. The precipitated solid was collected, washed with water, and dried under reduced pressure (1.66 g of crude product). The crude product was dissolved in a solution of sodium hydrogen carbonate (2.0 g) in water (100 mL), and reprecipitated with conc. hydrochloric acid. After drying under reduced pressure, the crude, dark brown solid amounted to 0.88 g (~150% theoretical yield of the required diacid). For further purification, the diacid was converted into its dimethyl ester and the ester hydrolysed to the acid as follows. The above crude product was suspended in methanol (125 mL) and the mixture was saturated at room temperature with dry hydrogen chloride (g), and then heated under reflux for 23 h. The resultant clear, green solution was evaporated under reduced pressure. The residue was extracted with dichloromethane (20 mL), and the dichloromethane was decanted from insoluble gummy material. This dichloromethane extract was purified by means of flash column chromatography (SiO_2/dichloromethane) to give the dimethyl ester as a cream-coloured solid (149 mg, 25%), mp 182–186°C. (Found: C, 73.5; H, 4.68%. $C_{18}H_{14}O_4$ requires C, 73.46; H, 4.79.%) ν_{max}/cm^{-1} (KBr) 1728, 1638, 1617; δ_H ($CDCl_3$) 4.03 (6H, s, 2×CO_2CH_3), 7.87 (2H, s, 2×Ar*H*), 8.32 (2H, dd, *J*=1.7 Hz and *J*= 8.6 Hz, 2×Ar*H*), 8.64 (2H, d, *J*=1.6 Hz, 2×Ar*H*), 8.76 (2H, d, *J*=8.6 Hz, 2×Ar*H*).

A suspension of the above dimethyl ester (143.3 mg, 0.487 mmol) in a mixture of ethanol (5 mL) and 20% aqueous sodium hydroxide solution (5 mL, 25.0 mmol) was heated under reflux for 1 h. Water (10 mL) was added, and refluxing was continued for a further 2 h. The resulting solution was evaporated under reduced pressure, and the residue was dissolved in water (50 mL). This solution was cooled in an ice bath, and acidified with conc. HCl. The precipitated solid was collected on a filter paper, washed with water, and dried under reduced pressure to give the required *phenanthrene dicarboxylic acid* (**13**) as a pale yellow powder (118 mg, 91%), mp >350°C (lit. [27] Mp 165–167°C); ν_{max}/cm^{-1} (KBr) 1692, 1686, 1654, 1639, 1617 cm^{-1}. δ_H (DMSO-d_6) δ 8.09 (2H, s, 2×Ar*H*), 8.22 (2H, dd, *J*=1.8 Hz and *J*=8.6 Hz 2×Ar*H*), 8.67 (2H, d, *J*=1.7 Hz, 2×Ar*H*), 8.99 (2H, d, *J*=8.7 Hz, 2×Ar*H*), 13.26 (2H, br, exch., 2×CO_2H).

Diethyl stilbene-4,4′-dicarboxylate[21] (18b). A mixture of 4-toluic acid (50 g, 368 mmol) and sulphur flowers (5.88 g, 184 mmol) was placed in a 1-litre conical flask, and stirred and heated on a sand tray at 260–275°C (just on the bp of the toluic acid) for 2 h. The resultant mixture was allowed to cool to about 140°C, and hot xylene (200 mL) was added. A reflux air-cooled condenser was fitted, and the mixture was boiled under reflux for 30 min., then filtered hot. The filter cake was boiled with dioxane (75 mL) for 30 min., then filtered, washed with hot dioxane (50 mL) and dried under reduced pressure to afford the crude dicarboxylic acid **18a** as a yellow powder (12.71 g). The crude product was taken up in a boiling solution of potassium hydroxide (7.0 g) in water (300 mL). Some insoluble yellow material was removed by filtration, and the filtrate was concentrated to 100 mL, then allowed to cool. The dipotassium salt crystallised out as yellow plates (11.86 g after drying). The dipotassium salt was taken up in boiling water (350 mL),

and the resultant solution was acidified while hot with conc. HCl (15 mL). The resultant precipitate was digested hot for 1.5 h, and after cooling the product was collected, washed with water, and dried under reduced pressure to give the required dicarboxylic acid **18a** as a pale yellow powder (9.09 g, 37% yield based on sulphur), mp >320°C (lit.[21] Mp 460°C, [sealed tube]).

Diethyl ester 18b.[21,22] The above dicarboxylic acid (8.623 g, 32.4 mmol) was refluxed with thionyl chloride (50 mL) for 20 h. The resultant mixture was evaporated under reduced pressure, and residual thionyl chloride was removed from the solid residue by co-evaporation with hexane (2×30 mL). Crystallisation from benzene gave the acid chloride as a bright yellow powder (2.79 g, 28% yield), mp 222–228°C (lit.[21] mp 228–232°C, lit.[22] mp 223–224°C). (*Note*: When this reaction was carried out on a smaller scale, but with a reflux period of just 15 h, the yield of acid chloride was improved to 44%.) The acid chloride (2.78 g) was refluxed with ethanol (100 mL) for 17 h. The solution was evaporated under reduced pressure, and the crystalline residue recrystallised from ethanol to give the required diester as pale yellow crystals (2.58 g, 87% yield), mp 129–133°C (lit.[21] mp 129.9–130°C, lit.[23] mp 130–131°C); δ_H ($CDCl_3$) 1.32 (6H, t, J=7.0 Hz, 2×CH_2–CH_3), 4.39 (4H, q, J=7.0 Hz, 2×O–CH_2–CH_3), 7.23 (2H, s, Ar–C*H*=C*H*–Ar), 7.59 (4H, m, Ar*H*), 8.06 (4H, m, Ar*H*).

Diethyl 3,6-phenanthrene dicarboxylate[21] (15b). A solution of diethyl 4,4′-stilbene dicarboxylate **18b** (0.5015 g, 1.546 mmol) in toluene (1 L) containing iodine (0.1240 g) was irradiated for 3 days using a medium-pressure mercury lamp (400 W) in a quartz tube while oxygen was slowly bubbled though the reaction mixture. After removal of the solvent under reduced pressure, the residue was taken up in dichloromethane and passed through a short column of silica gel. Concentration of the eluate followed by addition of methanol precipitated a white solid which, on recrystallization from a dichloromethane/methanol mixture, gave the required phenanthrene as white prisms (243 mg, 49% yield) mp 162–164°C (lit.[21] mp 164–166°C).

3,6-Phenanthrene dicarboxylic acid (15a). Diethyl 3,6-phenanthrene dicarboxylate (150 mg, 0.466 mmol) was suspended in a mixture of ethanol (5 mL) and aq. sodium hydroxide (1.0 g in water 15 mL, 25 mmol). The reaction mixture was heated under reflux for 3 h, then solvent was removed under reduced pressure. The residue was dissolved in water (25 mL), cooled in ice, and acidified with conc. hydrochloric acid to afford the required phenanthrene dicarboxylic acid as a white solid which was filtered, washed with water and dried (912 mg, 99%). Mp>250°C; ν_{max}/cm^{-1} (KBr) 2981, 2824, 2641, 1691, 1622, 1449, 1422, 1295, 1276; δ_H (DMSO-d_6): 8.08–8.23 (6H, m, ArH); 9.35 (2H, s, ArH); 13.25 (2H, s, 2×CO_2H); HREIMS: Found: 266.05877 Calculated for $C_{16}H_{10}O_4$ 266.05791.

Cyclopropane-*trans*-1,2-dicarboxylic acid.[12,13] Sodium hydroxide solution (1.015 g, 2.56 mmol in water 10 mL) was added with stirring to a solution of dimethyl *trans*-cyclopropane dicarboxylate (1.085 g, 6.86 mmol) in ethanol (5 mL). The clear solution was left standing at room temperature for 3 h then solvent was removed under reduced pressure at room temperature. Water was added and removed under reduced pressure at room temperature. Ether (25 mL) and water (50 mL) were added and the di-sodium salt was extracted. The organic layer was extracted again with water. The water extracts were combined and acidified with conc. hydrochloric acid (pH 2). Water was removed under reduced pressure at room temperature, then the white solid mass was triturated with ethyl acetate (100 mL, dry) and filtered. The filtrate was removed under reduced pressure at room temperature to give the required diacid as a white solid (0.885 g, 99% yield), mp 177–178°C. [lit.[12] mp 172–174°C; lit.[13] mp 175°C]. ν_{max}/cm^{-1} (KBr): 1695. δ_H(DMSO-d_6): 1.14–1.29 (2H, t, J=8.1 Hz); 1.85–1.91 (2H, t, J=7.5 Hz); 12.58 (2H, broad 2×CO_2H exch.).

Preparation of head to head linked dimers (target compounds)

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dimethylaminopropane} (19). (*dmap pyrr pyrr H2phen pyrr pyrr dmap*) The nitro dimer compound (**5a**, 554 mg) in isopropanol (50 mL) was hydrogenated at room temperature over 10% Pd–C (537 mg) for 4 h. The catalyst was removed by filtration through kieselguhr under an atmosphere of nitrogen, and the filtrate was evaporated under reduced pressure to give the crude amine as a pale grey coloured, brittle, glassy solid (424 mg, 83%). This material was dissolved in dry DMF (4.0 mL), and the resultant solution (containing ~100 mg per mL) was used immediately in the following coupling reactions:

Using HBTU/NMM: A mixture of dihydrophenathrene-2,7-dicarboxylic acid **14** (25.8 mg, 0.0963 mmol), HBTU (110 mg, 0.289 mmol), NMM (65 μL, 0.594 mmol) and dry DMF (1.5 mL) was placed under nitrogen and stirred at room temperature for 30 min. A 1.0 mL aliquot of the solution of the amine derived from **5a** (100 mg, 0.289 mmol) above was added, and the mixture was stirred at room temperature for 18 h. The product was isolated from the resultant solution using HPLC (see Experimental). The fractions containing the product were frozen immediately on collection, and then freeze dried to give required *linked oligomer* **19**, bis-TFA salt, as a cream-coloured solid (54% yield) which had no distinct mp (Found: ES-MS: 925.7, 462.8; $C_{50}H_{60}N_{12}O_6$ (free base) requires 926.10 (M+1), 463.56 [(M+2)/2]); δ_H (DMSO-d_6) δ 1.84 (4H, m, 2×CH_2–CH_2–CH_2), 2.77 (12H, s, 2×NMe_2), 2.97 (4H, s, CH_2–CH_2 bridge), 3.04 (4H, m, 2×CH_2–CH_2), 3.26 (4H, m, 2×CH_2–CH_2), 3.83 (6H, s, 2×pyrrole NCH_3), 3.89 (6H, s, 2×pyrrole NCH_3), 6.95 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 7.12 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 7.19 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 7.34 (2H, d, J=1.6 Hz, 2× pyrrole Ar*H*), 7.90 (2H, s, Ar*H*), 7.93 (2H,d, J=8.0 Hz, Ar*H*), 8.05 (2H, d, J=8.4 Hz, Ar*H*), 8.16 (2H, t, exch., 2×CON*H*–CH_2), 9.95 (2H, s, exch., 2×CON*H*), 10.37 (2H, s, exch., 2×CON*H*).

Using diisopropylcarbodiimide/HOBT: A 1.0 mL aliquot of the solution of the primary amine derived from **5a** (100 mg, 0.289 mmol) above was added to a mixture of the dihydrophenathrene dicarboxylic acid **14** (25.8 mg, 0.0963 mmol),

HOBT (26 mg, 0.1926 mmol) and dry DMF (1.0 mL). The resultant mixture was placed under nitrogen, and stirred and cooled in an ice bath. A solution of diisopropylcarbodiimide (54.5 mg, 0.4325 mmol) in dry DMF (0.5 mL) was added, and the resultant solution was allowed to come to room temperature. After 18 h, water (2 drops) was added. The required *linked oligomer* was isolated as described above (49% yield).

The following compounds were prepared similarly.

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dihydroxyethylaminopropane} (20). (*dheap pyrr pyrr H_2phen pyrr pyrr dheap*) In 45% yield from **5d** and dihydrophenanthrene-2,7-dicarboxylic acid using HBTU coupling. (Found: ES-MS: 1046.1, 523.9 $C_{54}H_{68}N_{12}O_{10}$ requires (free base) 1046.2 (M+1) and 523.6 [(M+2)/2]); ν_{max}/cm^{-1} (KBr) 1682, 1640, 1585, 1432, 1270, 1202; δ_H (DMSO-d_6) δ 1.91 (4H, m, 2×CH_2–CH_2–CH_2), 2.97 (4H, s, Ar–CH_2–CH_2–Ar), 3.17–3.24 (16H, m, 8×CH_2), 3.75 (8H, m, 4×CH_2), 3.82 (6H, s, 2× pyrrole NMe), 3.88 (6H, s, 2×pyrrole NMe), 5.30 (4H, bs, exch., 4×O*H*), 6.94 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.13 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.18 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.34 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.90–7.94 (4H, m, 4×benzene Ar*H*), 8.04–8.06 (2H, m, 2×benzene Ar*H*), 8.15 (2H, t, *J*=5.6 Hz, exch., 2×CON*H*–CH_2), 9.07 (2H, bs, exch., 2×TFA), 9.95 (2H, s, exch., 2×CON*H*), 10.34 (2H, s, exch., 2×CON*H*).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-*N*-pyrrolidinylpropane} (21). (*pyrp pyrr pyrr H_2phen pyrr pyrr pyrp*) In 65% yield from **5b** and dihydrophenanthrene 2,7-dicarboxylic acid using HBTU coupling. (ES-MS: found 978.0, and 488.94; $C_{54}H_{66}N_{12}O_6$ requires (M+1) 979.1 and [(M+2)/2] 489.59.); ν_{max}/cm^{-1} (KBr) 1679, 1648, 1535, 1439, 1266, 1201. δ_H (DMSO-d_6): 1.82–1.91 (8H, m, 4×CH_2); 2.02–2.04 (4H, m, 2×CH_2); 2.97–3.02 (8H, m and s, 2×CH_2 and dihydrophenanthrene 2×CH_2); 3.13–3.18 (4H, m, 2×CH_2); 3.24–3.27 (4H, m, 2×CH_2); 3.56–3.57 (4H, m, 2×CH_2); 3.82 (6H, s, 2×NMe pyrrole); 3.88 (6H, s, 2×NMe pyrrole); 6.96 and 6.97 (2H, d, *J*=1.6 Hz, pyrrole); 7.12 and 7.13 (2H, d, *J*=1.6 Hz, pyrrole); 7.17 and 7.18 (2H, d, *J*=1.6 Hz, pyrrole); 7.33 and 7.34 (2H, d, *J*=1.6 Hz, pyrrole); 7.90 (2H, s, ArH); 7.92 and 7.94 (2H, d, *J*=1.6 Hz, ArH); 8.09 and 8.07 (2H, d, *J*=1.6 Hz, ArH); 8.14–8.17 (2H, t, *J*= 5.6 Hz, CONH exch.); 9.4 (2H, broad, TFA exch.); 9.95 (2H, s, 2×CONH exch.); 10.37 (2H, s, 2×CONH exch.).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-Methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-(4-methylpiperazinyl)propane} (22). (*mpip pyrr pyrr H_2phen pyrr pyrr mpip*) In 43% yield from **5c** and dihydrophenanthrene 2,7-dicarboxylate using HBTU coupling. (ES-MS: Found: 1036.1, 518.1 $C_{56}H_{70}N_{14}O_6$ requires (M+1) 1036.2 and [(M+2)/2] 518.6; ν_{max}/cm^{-1} (KBr) 1680, 1641, 1538, 1437, 1267, 1200; δ_H (DMSO-d_6): 1.77 (4H, m, 2×CH_2); 2.72 (6H, s, 2×NMe); 2.97 (4H, s, dihydro); 3.23–3.24 (4H, q, *J*= 5.6 Hz, 2×CH_2); 3.53 (20H, broad); 3.82 (6H, s, 2×NMe pyrrole); 3.88 (6H, s, 2×NMe pyrrole); 6.95 (2H, s, pyrrole); 7.12 (2H, s, pyrrole); 7.16 (2H, s, pyrrole); 7.34 (2H, s, pyrrole); 7.90 (2H, s, ArH); 7.92 and 7.94 (2H, d, *J*= 8.4 Hz, ArH); 8.04 and 8.06 (4H, d, *J*=8.4 Hz, ArH and t, *J*=5.4 Hz, CONH exch.); 9.94 (2H, s, CONH exch.); 10.36 (2H, s, CONH exch.).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido) pyrrole-2-carboxamido]-morpholine} (23). (*morphp pyrr pyrr H_2phen pyrr pyrr morph*) In 67% yield from **5e** and dihydrophenanthrene-2,7-dicarboxylic acid **14** using HBTU coupling. (Found: ES-MS: 1010.0 and 505.0; $C_{54}H_{64}N_{12}O_8$ requires (free base) 1010.18 (M+1) and 505.60 [(M+2)/2]); ν_{max}/cm^{-1} (KBr) 1677, 1642, 1534, 1440, 1265, 1201; δ_H (DMSO-d_6) δ 1.89 (4H, m, 2×CH_2–CH_2–CH_2), 2.97 (4H, s, Ar–CH_2–CH_2–Ar), 2.97–3.14 (8H, m, 4×CH_2), 3.25 (4H, m, 2×CH_2), 3.40 (4H, m, 2×CH_2), 3.63 (4H, m, 2×CH_2), 3.83 (6H, s, 2×NMe), 3.88 (6H, s, 2×NMe), 3.98 (4H, m, 2×CH_2), 6.96 (2H, d, *J*=1.6 Hz, 2×Ar*H*), 7.12 (2H, d, *J*=1.6 Hz, 2×Ar*H*), 7.18 (2H, d, *J*=2.0 Hz, 2×Ar*H*), 7.34 (2H, d, *J*=2.0 Hz, 2×Ar*H*), 9.6–9.8 (2H, bs, exch., 2×TFA) 9.95 (2H, s, exch., 2×CON*H*), 10.37 (2H, s, exch., 2×CON*H*).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-propanamidine} (24). (*amidp pyrr pyrr H_2phen pyrr pyrr amidp*) In 35% yield from **5f** and dihydrophenanthrene-2,7-dicarboxylic acid **14** using HBTU coupling. (Found: ES-MS: 895.86 and 447.84; $C_{46}H_{50}N_{14}O_6$ (free base) requires: 895.99 (M+1) and 448.50 [(M+2)/2]); ν_{max}/cm^{-1} (KBr) 1682, 1640, 1585, 1540, 1270, 1202, 1134; δ_H (DMSO-d_6) δ 2.61 (4H, t, 2×CH_2–CH_2–C NH_4^+), 2.97 (4H, s, CH_2–CH_2 bridge), 3.51 (4H, q, *J*=6.0 Hz, becoming t, *J*=6.2 Hz after D_2O, 2×NH–CH_2–CH_2), 3.82 (6H, s, 2×pyrrole NCH_3), 3.88 (6H, s, 2×pyrrole NCH_3), 6.97 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.12 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.18 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.34 (2H, d, *J*=1.6 Hz, 2× pyrrole Ar*H*), 7.90 (2H, s, 2×Ar*H*), 7.93 (2H, d, *J*=8.4 Hz, 2×Ar*H*), 8.05 (2H, d, *J*=8.4 Hz, 2×Ar*H*), 8.20 (2H, t, *J*=5.6 Hz, exch., 2×CON*H*–CH_2), 8.53 (4H, s, exch., amidine), 8.90 (4H, exch., amidine), 9.95 (2H, s, 2×CON*H*), 10.37 (2H, s, 2×CON*H*).

Phenanthrene-3,6-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dimethylaminopropane} (25). (*dmap pyrr pyrr phen pyrr pyrr dmap*) In 69% yield from **5a** and phenanthrene-3,6-dicarboxylic acid **15a** using HBTU coupling. (Found: ES-MS: 924.2 and 462.9 $C_{50}H_{58}N_{12}O_6$ (free base) requires 924.1 (M+1) and 462.5 [(M+2)/2]); ν_{max}/cm^{-1} (KBr) 1682, 1649, 1535, 1270, 1201; δ_H (DMSO-d_6) 1.85 (4H, qt, *J*=8.0 Hz, 2×CH_2–CH_2–CH_2), 2.80 (12H, d, *J*=2.8 Hz, becoming s after D_2O, 2×$NH^+(CH_3)_2$), 3.08 (4H, m, becoming t, *J*=5.6 Hz after D_2O, 2×NH–CH_2–CH_2), 3.26 (4H, q, *J*=6.8 Hz, becoming t, *J*=5.6 Hz after D_2O, 2×NH–CH_2–CH_2), 3.83 (6H, s, 2×pyrrole NCH_3), 3.91 (6H, s, 2×pyrrole NCH_3), 6.97 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.18 (2H,d, 2×pyrrole Ar*H*), 7.19 (2H, d, *J*=1.6 Hz, 2×pyrrole Ar*H*), 7.40 (2H, d, *J*=1.6 Hz, 2× pyrrole Ar*H*), 8.06 (2H,s, Ar*H*), 8.17 (2H, t, *J*=5.6 Hz, exch.,

2×CONH–CH_2), 8.28 (2H,d, J=2.1 Hz, 2×ArH), 8.63 (2H, d, J=2.0 Hz, 2×ArH), 9.05 (2H, d, J=4.5 Hz, 2×ArH), 9.28 (2H, br, exch., 2×NH^+), 9.98 (2H, s, exch., 2×CONH), 10.60 (2H, s, exch., 2×CONH).

Using HATU/NMM: A mixture of **15a** (25.6 mg, 0.0963 mmol), HATU (115 mg, 0.303 mmol), NMM (65 μL, 0.594 mmol) and dry DMF (1.5 mL) was placed under nitrogen and stirred at room temperature for 30 min. A 1.0 mL aliquot of the solution of the primary amine derived from **5a** (100 mg, 0.289 mmol) above was then added, and the mixture was stirred at room temperature for 18 h. Yield 80.7 mg (73%).

Bisbenzothiophene-3,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dimethylaminopropane} (26). (*dmap pyrr pyrr dbthi pyrr pyrr dmap*) In 62% yield from **5a** and bisbenzothiophene-3,7-dicarboxylic acid **11** using HBTU coupling. (Found: ES-MS: 929.8, 465.6; $C_{48}H_{56}N_{12}O_6S$ requires: (M+1) 929.85, [(M+2)/2] 464.9). δ_H (DMSO-d_6): 1.82–1.86 (4H, qt, J=6.8 Hz, 2×CH_2); 2.78 (12H, s, 2×NMe_2); 3.04–3.08 (4H, t, J=7.2 Hz, 2×CH_2); 3.23–3.32 (4H, q, J=6.8 Hz, 2×CH_2); 3.83 (6H, s, 2×NMe pyrrole); 3.90 (6H, s, 2×NMe pyrrole); 6.96 and 6.97 (2H, d, J=1.6 Hz); 7.15 (2H, d, J=1.6 Hz); 7.19 (2H,d, J=1.6 Hz); 7.37 (2H, d, J=1.6 Hz); 8.11 and 8.12 (2H, d, J=8.0 Hz); 8.14–8.18 (2H, t, J=6.0 Hz,CONH exch); 8.59 and 8.61 (2H. d, J=8.0 Hz); 8.65 (2H, s); 9.30 (2H, broad, 2×TFA exch.); 9.9 (2H, s, CONH exch); 10.54 (2H, s, CONH exch.).

Fluorenone-3,6-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dimethylaminopropane} (27). (*dmap pyrr pyrr fluo pyrr pyrr dmap*) In 45% yield from **5a** and fluorenone-3,6-dicarboxylic acid **12** using HBTU coupling. (Found: ES-MS: 925.8, 462.7 $C_{49}H_{56}N_{12}O_7$ requires (M+1) 926.1; [(M+2)/2] 463.5). δ_H (DMSO-d_6): 1.81–11 (4H, qt, J=8.0 Hz, 2×CH_2); 2.79 (12H, s, 2×Me_2); 3.06–3.10 (4H, t, J=7.8 Hz, 2×CH_2); 3.23–3.26 (4H, q, J=6.4 Hz, CH_2); 3.83 (6H, s, 2×pyrrole-Me); 3.89 (6H, s, 2×pyrrole-Me); 6.96 and 6.96 (2H, d, J=1.6 Hz, ArH); 7.14 (2H, d, J=1.6 Hz, ArH); 7.18 and 7.19 (2H, d, J=1.6 Hz, ArH); 7.35and 7.36 (2H, d, J=1.6 Hz, ArH); 8.06 and 8.08 (2H, d, J=8.4 Hz, ArH); 8.14–8.17 (2H, t, J=8.4 Hz, 2×NH exch.); 8.27–8.28 (4H, m, ArH); 9.27 (2H, broad, TFA exch.); 9.97 (2H, s, 2×NH exch.); 10.56 (2H, s, 2×NH exch.).

1,4-Benzenedicarboxamido{3-[1-Methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2 carboxamido]-dimethylaminopropane} (28). (*dmap pyrr pyrr tere pyrr pyrr dmap*) In 34% yield from **5a** and terephthalic acid using HBTU coupling. (Found: ES-MS 824.0, 412.8; $C_{42}H_{54}N_{12}O_6$ requires: (M+1) 823.68, [(M+2)/2] 412.84); ν_{max}/cm^{-1} (KBr) 1680, 1642, 1538, 1267, 1200; δ_H (DMSO-d_6): 1.82–1.86 (4H, qt, J=8.0 Hz, 2×CH_2); 2.79 (6H, s, 2×NMe); 2.80 (6H, s, 2×NMe); 3.05–3.10 (4H, m, 2×CH_2); 3.22–3.27 (4H, m, 2×CH_2); 3.82 (6H, s, 2×NMe pyrrole); 3.88 (6H, s, NMe pyrrole); 6.95 and 6.96 (2H, d, J=2.0 Hz); 7.12 and 7.13 (2H, d, J=1.6 Hz); 7.18 (2H, d, J=1.6 Hz); 7.35 (2H, d, J=1.6 Hz); 8.06 (4H, s); 8.14–8.17 (2H, t, J=5.6 Hz, CONH exch.); 9.35 (2H, broad TFA exch.); 9.95 (2H, s, 2×CONH exch.); 10.47 (2H, s, 2×CONH exch.).

***Trans*-cyclopropane-1,2-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2 carboxamido]-dimethylaminopropane} (30).**[6] (*dmap pyrr pyrr cycp pyrr pyrr dmap*) In 46% yield from **5a** and *trans*-cyclopropane 1,2-dicarboxylic acid using HBTU coupling. (Found: ES-MS 787.0, 393.6. $C_{39}H_{54}N_{12}O_6$ requires (M+1) 787.65; [(M+2)/2] 394.5); ν_{max}/cm^{-1} (KBr) 1682, 1649, 1582, 1535, 1438, 1201; δ_H (DMSO-d_6): 1.21–1.24 (2H, t); 1.81–1.85 (4H, qt, J=7.9 Hz); 2.18–2.21 (2H, t, J=7.2 Hz); 2.77 (12H, s, 2×NMe_2); 3.03–3.07 (4H, t, J=8.0 Hz); 3.21–3.26 (4H, q, J=6.4 Hz); 3.81 (6H, s, 2×NMe pyrrole); 3.82 (6H, s, 2×NMe pyrrole); 6.85 and 6.86 (2H, d, J=2.0 Hz); 6.92 and 6.93 (2H, d, J=2.0 Hz); 7.15–7.17 (4H, dd, J=1.6 Hz and J=2.0 Hz); 8.12–8.15 (2H, t, J=5.6 Hz, CONH exch.); 9.50 (2H, broad TFA exch.); 9.86 (2H, s, CONH exch.); 10.24 (2H, s, CONH exch.).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[1-methyl-4-(4-amino-1-methyl-imidazol-2-carboxamido)imidazol-2-carboxamido]-dimethylaminopropane} (36). (*dmap imid imid H_2phen imid imid dmap*) In 5% yield from **6** and dihydrophenanthrene-2,7-dicarboxylic acid **14** using HBTU coupling. (Found: ES-MS: 929.7, 464.8 $C_{46}H_{57}N_{16}O_6$ requires (M+1) 930.1 and [(M+2)/2] 465.5); ν_{max}/cm^{-1} (KBr) 1677, 1641, 1582, 1405, 1265, 1200; δ_H (DMSO-d_6): 1.81–1.85 (4H, qt, J=3.6 Hz); 2.79 (6H, s, 2×NMe_2); 2.77 (6H, s, 2×NMe_2); 2.92 (4H, s); 3.03–3.07 (4H, t, J=18.8 Hz); 3.21–3.26 (4H, q, J=8.0 Hz); 3.97 (6H, s, 2×NMe_2 imidazole); 4.04 (6H, s, 2×NMe_2 imidazole); 7.56 (2H, d, J=4.8 Hz); 7.68 (2H, d, J=4.4 Hz); 7.96–8.07 (6H, m, ArH); 8.45–8.47 (2H, t, J=6.0 Hz, CONH exch.); 9.27 (2H, s, TFA exch.); 9.41 (2H, s, CONH exch.); 10.88 (2H, s, CONH exch.).

9,10-Dihydrophenanthrene-2,7-dicarboxamido{3-[2-(4-amino-1-methyl-pyrrole-2-carboxamido)thiazol-4-carboxamido]-dimethylaminopropane} (37). (*dmap thia pyrr H_2phen thia pyrr dmap*) In 40% yield from **8** and dihydrophenanthrene 2,7-dicarboxylic acid **14** using HBTU coupling. (Found: ES-MS: 962.01, 481.90. $C_{48}H_{56}O_6N_{12}S_2$ requires: (M+1) 962.20, [(M+2)/2] 481.60).); ν_{max}/cm^{-1} (KBr) 1680, 1647, 1538, 1397, 1203, 1130; δ_H (DMSO-d_6): 1.84–1.90 (4H, qt, J=6.7 Hz, 2×CH_2); 2.54 (6H, s, thiazole Me); 2.67 (6H, s, 2×NMe); 2.79 (6H, s, 2×NMe); 2.97 (4H, s, dihydrophenanthrene); 3.06–3.10 (4H, q, J=6.8 Hz, 2×CH_2); 3.11–3.27 (4H, m, 2×CH_2); 3.93 (6H, s, 2×NMe pyrrole); 7.45 (2H, s, pyrrole); 7.60 (2H, s, pyrrole); 7.92 (2H, s, ArH); 7.93 and 7.95 (2H, d, J=1.9 Hz, ArH); 8.05–8.11 (4H, s and t, J=4.8 Hz, ArH and {CONH exch.}); 9.24 (2H, broad, exch.); 10.47 (2H, s, CONH exch.); 12.48 (2H, s, CONH exch.).

Phenanthrene-3,6-dicarboxamido{3-[glycyl-1-methyl-4-(4-amino-1-methyl-pyrrole-2-carboxamido)pyrrole-2-carboxamido]-dimethylaminopropane} (38). (*dmap pyrr pyrr gly phen gly pyrr pyrr dmap*) In 49% yield from **5j** and dihydrophenanthrene-3,6-dicarboxylic acid **15a** using HBTU coupling. (Found: ES-MS: 1037.9 $C_{54}H_{64}N_{14}O_8$ requires (free base) (M+1) 1038.2 and [(M+2)/2]

2519.6); ν_{max}/cm^{-1} (KBr) 1678, 1647, 1582, 1534, 1266, 1201; δ_H (DMSO-d_6) 1.83 (4H, m, 2×CH_2–CH_2–CH_2), 2.78 (12H, d, J=2.8 Hz, becoming, s, after D_2O, 2×$NH^+[CH_3]_2$), 3.06 (4H, m, 2×N–CH_2–CH_2), 3.24 (4H, m, 2×N–CH_2–CH_2), 3.80 (6H, s, 2×pyrrole NMe), 3.83 (6H, s, 2×pyrrole NMe), 4.13 (4H, d, J=5.6 Hz, becoming, s, after D_2O, 2×NH–CH_2–CO), 6.92 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 6.95 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 7.15 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 7.19 (2H, d, J=1.6 Hz, 2×pyrrole Ar*H*), 8.04 (2H, s, Ar*H*), 8.16 (6H, m, becoming 4H after D_2O, 2×CON*H*CH_2 plus 4×Ar*H*), 9.24 (2H, t, J=5.6 Hz, exch., 2×CON*H*CH_2), 9.35 (2H, bs, exch., 2×TFA), 9.48 (2H,s, 2×Ar*H*), 9.86 (2H, s, exch., 2×CON*H*), 10.01 (2H, s, exch., 2×CON*H*).

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